REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on October 17, 2007, and the references cited therewith. Claims 1-59 are pending in this application.

Priority

Regarding Priority on page 3 of the October 17, 2006 Office Action, the Examiner states that the priority application 10/224,268 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application traverses the rejection of priority.

The '268 application provides numerous teachings and examples that provide adequate support or enablement in the manner provided for by first paragraph 35 U.S.C. 112 for one or more claims of the present application (see for example page 8, line 10 through page 10, line 11; and page 10, line 13 through page 22, line 13)..

Double Patenting Rejection

Regarding the Double Patenting rejection on page 4 of the October 17, 2006 Office Action, the Examiner rejected claims 8-20 and 27-45 as provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 10/224,268. Applicant traverses the rejection.

Claims 8-20 and 27-45 can be infringed without infringing claim 1 of copending Application No. 10/224,268 since a composition having a bone morphogenic protein sequence in the X position of the formula would not infringe the composition of claim 1 of 10/224,268. The MPEP at §804A states that a statutory Double Patenting rejection is not appropriate if there is an embodiment of the invention that falls within the scope of one claim, but not the other. For example, the invention defined by a claim reciting a compound having a halogen subtituent is not the identical or substantively the same as the compound except having a chlorine substituent in place of the halogen because halogen is broader than chlorine. See *In re Vogel*, 422 F.2d 438, (CCAP 1970). Claims 8-20 and 27-45 are not the same claim scope as the claims in the '268 Application as the Examiner points out in the Priority rejection. Therefore, Applicant respectfully requests withdrawal of the Double Patenting Rejection.

'112 Rejection of the Claims

Written Description

The Examiner rejected claims 8-20 and 27-45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically the Examiner states that claim 8 is drawn to a heparin-binding growth factor (HBGF) analog making claim 8 a genus claim. The Examiner further states that the specification and claim do not indicate what distinguishing attributes are shared by the members of the genus. Applicant traverses the Examiner's rejection.

The specification clearly states that the members of the genus all share the feature of binding selectively to heparin (line 5, page 11) and all share the feature of incorporating a growth factor sequence that binds to a growth factor receptor with examples of growth factors provided at line 9, page 11-line 10, page 12, or an analogue thereof. Similarly, the abstract of the invention states, "The invention provides synthetic heparin-binding growth factor analogs having at least one peptide chain that binds a heparin-binding growth factor receptor, covalently bound to a hydrophobic linker, which is in turn covalently bound to a non-signaling peptide that includes a heparin-binding domain." The Y domain is further cited in the specifications to be hydrophobic. Thus, all members of the genus share the features of A) peptide chains that binds a heparin-binding growth factor receptor, B) a hydrophobic linker, and C) a heparin-binding domain, and each of these features, or domains, is required.

The Examiner further states that the specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions, and/or additions that may be made to the polypeptide and does not clearly define analogs for any of the heparin-binding growth factor. Applicant traverses this statement as the Applicant clearly states in the specification at page 14 lines 20-27 that the analogue binds to its cognate partner growth factor receptor or a different growth factor receptor. For example, "Each synthetic heparin-binding growth factor analog of the invention is an analog of a particular heparin-binding growth factor (HBGF) that binds to one or more of the receptors bound by the particular HBGF." Thus, the limitation is set as receptor binding. Those skilled in the art would appreciate that given receptor binding as the central limitation, then amino acid substitutions, deletions, insertions, and/or additions could be used to modify the nature of that receptor binding. The Applicant points out that the receptor binding

sequences used in the invention can be derived from known natural receptor-binding sequences or those derived from processes such as phage display, yet again these sequences are delimited by their ability to bind cognate receptors. Furthermore, the peptides of this invention are limited in the invention to polypeptides containing three specific components: A) peptide chains that bind a heparin-binding growth factor receptor, B) a hydrophobic linker, and C) a heparin-binding domain. The invention specifies amino acid residue minimums and maximums for each of the three domains comprising the invention and specifying receptor binding for all of the analogs.

Further, the specification as originally filed includes a teaching of homologous sequences and percent homology preferred. (See for example page 15 lines 1-16.) Further, the MPEP at 2163 (I) states that the written description requirement addresses whether the original application provides adequate support for the claims at issue or whether the material added to the specification incorporates new matter in violation of 350 U.S.C. §132. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed.

Enablement Requirement

Regarding rejection of claims 8-20 and 27-45 under 35 U.S.C. 112 first paragraph on page 6, Applicant traverses the rejection.

The Examiner states that the breadth of claims 8-20 and 37-45 is too large since the specification fails to provide any guidance on how to produce other compounds of Formula II that retain the function of F2A4. The Applicant in the Background section points to scientific literature in Ray et al., Proc. Natl. Acad. Sci. USA 94: 7047-7052 (1997) and Ballinger et al., Nature BioTechnology 17: 1199-1204 (1999), among others including patent literature, that have been used to identify peptide receptor binding domains. It would be obvious to those skilled in the art that such methods could be used to identify additional receptor binding sequences which would be incorporated into the current invention. It would further be obvious to those skilled in the art that a" cassette" approach could be used to produce other compounds of Formula II by keeping constant the given a heparin-binding domain and hydrophobic linker and rotating the peptide chains that binds a heparin-binding growth factor receptor to change receptor specificity.

IV. Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

The following two subsections are presented below:

- IV(A.) Governing law and USPTO patent examining procedure on enablement (35 U.S.C. §112, paragraph 1)
- IV(B.) Point-by-point rebuttal of Examiner's asserted Wands' factors analysis

IV(A.) Governing law and USPTO patent examining procedure on enablement (35 U.S.C. §112, paragraph 1)

The governing law and United States Patent and Trademark Office ("USPTO") practice regarding the enablement requirement is provided, in pertinent part, below with reference to the Manual of Patent Examining Procedure.

From MPEP 2164.01 Test of Enablement

> *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.").
>
> A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

From MPEP 2164.01 Undue Experimentation

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain*

Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

From MPEP 2164.02 Working Example

NONE OR ONE WORKING EXAMPLE

When considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. In other words, lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. However, a rejection stating that enablement is limited to a particular scope may be appropriate.

The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence **and** state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.

[Emphasis added in double-underline and bold.]

From MPEP 2164.03 Relationship of Predictability of the Art and the Enablement Requirement [R-2]

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

From MPEP 2164.04 Burden on the Examiner Under the Enablement Requirement [R-1]

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the

claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing **and** why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

[Emphasis added in double-underline and bold.]

From MPEP 2164.05(b) Specification Must Be Enabling to Persons Skilled in the Art

The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. Where different arts are involved in the invention, the specification is enabling if it enables persons skilled in each art to carry out the aspect of the invention applicable to their specialty. *In re Naquin*, 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968).

From MPEP 2164.06 Quantity of Experimentation

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is

required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489 [sic, 498], 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

I. EXAMPLE OF REASONABLE EXPERIMENTATION

In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation.

From MPEP 2164.08 Enablement Commensurate in Scope With the Claims [R-2]

> All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
>
> In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
>
> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Point-by-point rebuttal of the Examiner's asserted Wands' factors analysis

The Examiner's case for the alleged nonenablement of the presently claimed invention has been set forth with reference to the factors summarized in *In re Wands* for considering whether undue experimentation is required to practice the full scope of a patent claim. (Office Action, page 6, ll. 13-18.)

[Applicants rebut each of the Examiner's assertions with respect to the Wand's factors in the following paragraphs. For convenience, the sections below are numbered similarly to the sections presented on pages 6-9 the Office Action.]

(1.) The breadth of the claims

The Examiner has asserted that the breadth of the claims is broad since the specifications fails to provide any guidance on how to produce other compounds of Formula II that retain the function of F2A4. (Office Action, page 6, l. 20-23.)

The present assertion by the Examiner is rebutted for the following reasons.

First, Applicants provide detailed teaching as to the criteria for producing other compounds of formula II which are discussed in the Written Description rejection above

Second, Applicant wish to point out that the independent claims do not recite that the activity of the Formula II compounds have an activity to the full force and effect as that of F2A2. Fig 6 demonstrates that, recombinant FGF, F2A4 and F2A3 synthetic compounds all have mitogenic activity. Similarly FGF, F2A4 and F2A3 also provide radioprotection as illustrated in Fig. 10. Therefore, the Examiner has not provided support for the statement that "F2A4, for example, has been shown in the instant Specification to function quite unlike full-length FGF2 as well as the other two growth factor analogs based on . . . Formula II." (See page 7, ll. 2-4).

Indeed, as cited in MPEP 2164.08 Enablement Commensurate in Scope With the Claims [R-2], in *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the Court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Unpredictability of the art

The Examiner has asserted that "although the disclosed compounds share several common structural features, relevant art (see below) shows that members of a class having structural homologies in common do not always share specific and substantial functional attributes or utilities." (Office Action, page 7, ll. 6-14.)

The present assertion by the Examiner is rebutted for the following reasons.

First, with respect to the alleged unpredictability regarding amino acid sequence of the functional peptide, Applicants again reiterate that the X portion of the analogue binds to a heparin binding growth factor (HBGF) receptor and/or has homology as defined on page 15, ll. 1-9, to the cognate peptide for the receptor as described on page 14 lines (20-27) of the

Specification. The sequences are known and are described in the database found at the world wide web address ncbi.nlm.nih.gov/entrez. The Z portion of the HBGF analogue contains one or more heparin binding motifs (see page 18 lines 15-22 and page 19, lines 5-21) and therefore binds to heparin. These features are not variable except as may be provided by the equivalents to which the claims are entitled. Thus, with respect to the critical features of the invention, the amino acid sequence is actually highly predictable.

Still further, as the Court stated in *In re Vaek*, 947 F.2d 488, 496, (Fed. Cir. 1991):

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218 (CCPA 1976).* However, there must be sufficient disclosure, either through illustrative examples or terminology, and to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.
>
> [Emphasis added in double-underline.]

As described above, the knowledge within the art and the originally filed specification each provided assays that allowed a skilled worker, during the relevant time period, to routinely and rapidly determine which HGBF analogues within the scope of the claims have or do not have mitogenic activity. Thus, as instructed by the cited passage of *In re Vaek,* the presently claimed invention must be found to be enabled.

The quantity of experimentation necessary

The Examiner states that due to the large quantity of experimentation necessary to determine an activity or property of the claimed HBGF compounds such that it can be determined how to use the claimed compounds and to screen for activity, the lack of direction/

guidance presented in the specification regarding same, the absence of working examples directed to same, the complex the breadth of the claims which fail to recite particular biological activities-undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The present assertion by the Examiner is rebutted for the following reasons.

First, Applicant wishes to point out that the standard of enablement with respect to undue experimentation and the quantity of experimentation is set forth in the MPEP as follows:

> **MPEP 2164.01 UNDUE EXPERIMENTATION**
>
> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).
>
> **MPEP 2164.06 Quantity of Experimentation**
>
> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489 [sic, 498], 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

> In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

Second, in view of the applicable standards presented above, Applicants wish to point out that (i.) making the peptides recited in the present claims was, as disclosed in the originally filed specification and discussed hereinabove, a routine matter achievable by conventional peptide synthesis technology as of the filing date and earliest U.S. priority date of the present application, as discussed above. Functional assays for testing peptides as discussed in the Specification for radioprotection and mitogenic activity are described in the originally filed application and also were known to those skilled in the art, as discussed in the Specification.

With respect to the assays disclosed in the originally filed specification, MPEP 2164.06 states:

> In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis

With respect to the present application, the assays for evaluating mitogenic stimulating activity are not particularly complicated, involve well established criteria, and do not require an extended period of time to generate results. Accordingly, *in arguendo,* even if some inoperable embodiments were within the scope of the present claims, a skilled worker was able, during the relevant time period, to rapidly evaluate various peptides according to the claims for their ability

for mitogenic activity and their ability to cause expression of similar differentiated phenotypes in an appropriate cell line using only routine procedures.

Given the mature state of peptide synthesis technology at the earliest U.S. priority date and the assays described in the originally filed specification, it cannot be seen how a skilled worker would have had to resort to undue experimentation to identify active peptides for use according to the claims.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (505 998 6134) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 13-4213

Respectfully submitted,

Janeen Vilven, Reg. No. 47,156
Direct line (505) 998-6134

PEACOCK MYERS, P.C.
Attorneys for Applicants
Post Office Box 26927
Albuquerque, New Mexico 87125-6927
Telephone: (505) 998-6134
Facsimile: (505) 243-2542
Customer No.: 005179